REMARKS

Claims 1-125 and 128-175 are pending the application. Claims 1-123, 125, 128-162 and 165 were previously canceled. Claims 126 and 127 were previously withdrawn as being directed to non-elected subject matter. Applicants hereby expressly reserve their right to prosecute the canceled and withdrawn claims in a separate application. Claims 124, 163-164, and 166-175 are currently under consideration. With the entry of this Response, Applicants have amended Claims 124 and 172. Applicants submit that the amendments to these claims do not add new matter.

Claim 124 was amended to recite a "method of reducing complement activation during gene therapy in a subject, comprising administering a composition comprising a viral vector comprising a complement modulator displayed on the surface of the vector, wherein the complement modulator inhibits complement activation and wherein the complement modulator is encoded by the viral vector." Support for the amendments to Claim 124 can be found at least in paragraphs [0113], [0116], [0120]-[0125], [0275], and [0302] of the published application (US 2007/0036721).

Claim 172 was amended to redress a misspelled word. Support for the amendment to Claim 172 can be found at least at paragraph [0104] of the published application (US 2007/0036721).

Claim 124 is an independent claim. In view of the subsequent remarks regarding this independent claim, Applicants respectfully request allowance of all the pending claims.

OBJECTION OF THE SPECIFICATION

The Office Action objected to the title of the present application for not referring to the claimed method. (Office Action, p. 3). With the entry of this Response, Applicants have amended the Specification by amending the title. Applicants respectfully submit that this objection is moot in view of Applicants' amendments, and request that the Examiner withdraw this objection.

CLAIM OBJECTIONS

The Office Action objected to Claims 124, 126-127, 163-164, and 166-175. The objection is based on Claim 124's recitation of "expressed on the surface of the vector." The Office Action stated, that "in actuality, the modulator is displayed on the surface." (Office Action, pp. 3-4). Applicants have amended Claim 124 to recite "a complement modulator displayed on the surface of the vector." Applicants respectfully submit that this objection is moot in view of Applicants'

amendments, and request that the Examiner withdraw this objection and allow these claims.

REJECTION UNDER 35 U.S.C. § 112, SECOND PARAGRAPH

The Office Action rejected Claims 124, 126-127, 163-164, and 166-175 under 35 U.S.C § 112, second paragraph, as allegedly being indefinite. (Office Action, p. 4). Applicants respectfully traverse this rejection to the extent that the rejection applies to the claims as amended.

With respect to independent Claim 124, the Office Action stated that the "metes and bounds are not clear." (Office Action, p. 4). Specifically, the Office Action stated that "the vector is not 'expressed' on the surface of the vector, but is displayed on the surface." With the entry of this Response, Applicants first note that Claim 124 has been amended to recite "a complement modulator displayed on the surface of the vector." Also with respect to independent Claim 124, the Office stated that the recitation of "in gene therapy" did not clearly convey whether a gene therapy protocol is required to take place. (Office Action, p. 4). With the entry of this Response, Applicants note that they have further amended Claim 124 to recite "A method of reducing complement activation during gene therapy in a subject, comprising. . . ."

In addition to the amendments and in response to the Office Action's allegations, Applicants direct the Examiner's attention the Specification that makes clear the metes and bounds of the instantly amended claims. Specifically, Applicants direct the Examiner's attention to portions of the Specification which explains: (1) that "inhibition of complement activation has the added benefit of decreasing the humoral and cell mediated immune response to virus," (2) that "inhibition of complement can be used to reduce redirection of the vector, thereby allowing its concentration in a desired location," (3) that "innate and systemic immunity can be considered in the design of the vector," (4) that "two general strategies exist for the reduction of immune activation that accompany viral vector delivery," and (5) that "the vectors disclosed herein can decrease these effects for gene therapy vectors." (*See* Specification paragraphs [0113], [0116], [0121], [0123], [0124], [0275], and [302]). Applicants respectfully submit that at least these cited portions of the Specification make clearly convey to one of skill in the art the claimed methods and more specifically the metes and bounds of the claimed methods. Specifically, Applicants submit that one of skill in the are would understand that the claimed methods and compositions can be used in gene therapy and therefore would easily understand the metes and bounds of the current claims.

Applicants therefore respectfully submit that this rejection is moot in view of Applicants' amendments and arguments, and request that the Examiner withdraw this rejection and allow claims 124, 126-127, 163-164, and 166-175.

REJECTION UNDER 35 U.S.C. § 112, FIRST PARAGRAPH

The Office Action rejected the claims for allegedly failing to comply with the written description requirement. Specifically, the Office Action stated that several claimed elements constituted new matter.

Prior to addressing each specific rejection, Applicants note that M.P.E.P. § 2164.04 states that "a description as filed is presumed to be adequate unless or until sufficient evidence or reasoning to the contrary has been presented by the examiner to rebut the presumption." To rebut this presumption, the examiner "has the initial burden of presenting by a preponderance of evidence why a person skilled in the art would not recognize in an applicant's disclosure a description of the invention defined by the claims." Thus, the M.P.E.P. charges the examiner with providing a reasonable basis to reject a claim for failing to satisfy the written description requirement. This burden requires "a full development" of the reasons showing that, by a preponderance of the evidence, a person of ordinary skill in the art would not recognize a description of the claimed invention in the disclosure. In this regard, the M.P.E.P. expressly instructs that merely conclusory statements are insufficient. Rather, every written description rejection "should be stated with a full development of the reasons rather than by a mere conclusion . . . ." (M.P.E.P. § 706.03). Stated another way, the Office must adequately explain the perceived shortcomings of the application so that Applicants are properly notified and able to respond. Finally, until the Office establishes a *prima facie* case, Applicants are not under an obligation to rebut the rejection. (M.P.E.P. § 2163.04). Applicants respectfully submit that such is the case here.

When a disclosure describes a claimed invention in a manner that permits one skilled in the art to reasonably conclude that Applicants possessed the claimed invention, then the written description requirement is satisfied. (M.P.E.P. § 2163). This possession may be shown in any number of ways and Applicants need not describe every claim feature exactly because there is no *in haec verba* requirement. (M.P.E.P. § 2163). Rather, to satisfy the written description requirement, all that is required is "reasonable clarity." (M.P.E.P. § 2163.02). Also, an adequate description may be

made in any way through express, implicit, or even inherent disclosures in the application, including words, structures, figures, diagrams, and/or formulae. (M.P.E.P. §§ 2163(I), 2163.02). Furthermore, Applicants need not disclose in detail, and preferably omits, that which is conventional or well known in the art. (M.P.E.P. § 2163(II)(A)(2)). Finally, it is important to be mindful of the generally inverse correlation between the level of skill and knowledge in the art and the specificity of disclosure necessary to satisfy the written description requirement. (M.P.E.P. § 2163(II)(A)(2)).

1. Written Description – "in gene therapy"

The Office Action rejected Claims 124, 163-164, and 166-175 under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the written description requirement. Specifically, the Office Action stated that the recitation of "in gene therapy" by these claims constituted new matter. (Office Action, p. 5). Applicants respectfully traverse this rejection to the extent that the rejection applies to the claims as amended.

Applicants respectfully submit that the Office Action fails to meet its burden to articulate a "reasonable basis challenging the adequacy of the written description" with "findings of fact." The Office Action has not demonstrated how a person skilled in the art would not have understood Applicants to have been in possession of the claimed methods and compositions for use in gene therapy. Consequently, Applicants are under no burden to rebut this rejection. (M.P.E.P. §§ 706.07, 2163, 2163.04). For this reason, Applicants traverse the rejection and respectfully request that the Examiner withdraw the rejection of these claims.

Nevertheless, to expedite the prosecution of these claims to allowance, Applicants now address the Office Action's specific statements.

The Specification demonstrates that Applicants had possession of viral vectors for use "in gene therapy." The Specification explains at least the following: (1) that "inhibition of complement activation has the added benefit of decreasing the humoral and cell mediated immune response to virus," (2) that "inhibition of complement can be used to reduce redirection of the vector, thereby allowing its concentration in a desired location," (3) that "innate and systemic immunity can be considered in the design of the vector," (4) that "two general strategies exist for the reduction of immune activation that accompany viral vector delivery," and (5) that "the vectors disclosed herein can decrease these effects for gene therapy vectors." (*See* paragraphs [0113], [0116], [0121], [0123],

[0124], [0275], and [302]).

The Examiner appears to take issue with the fact that the vector itself is not required to carry a transgene and it appears that complement is inhibited by the vector (Our summary of the Office Action's comments on pages 5 and 6 of the current Office Action). This is precisely what Applicants are currently claiming. Complement is inhibited by the display of the complement modulator on the surface of the vector. Gene therapy is NOT required for complement inhibition. The reference to "gene therapy" is simply a reference to one use of the disclosed vectors and methods. The Examiner himself has recognized as much (See Office Action, page 5, lines 20-22)

In view of the description discussed above, Applicants submit that the Specification permits one of skill in the art to reasonably conclude that Applicants understood that the claimed methods and compositions could be used during gene therapy to reduce complement activation. When considered in its entirety and coupled with the state of the art at the time of filing, Applicants' Specification describes the claimed invention in sufficient detail so that one skilled in the art would reasonably conclude that Applicants had possession of the claimed methods and compositions. Thus, the written description requirement is satisfied. Applicants respectfully request that the Examiner withdraw this rejection and allow these claims.

2. Written Description – "gene of interest"

The Office Action rejected Claims 124, 163-164, and 166-175 under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the written description requirement. Specifically, the Office Action stated that the recitation of "gene of interest" by these claims constituted new matter, and that the cited paragraphs do not provide support for a "generic gene of interest." (Office Action, p. 7). Furthermore, the Office Action also stated (1) that a viral vector comprising a gene of interest is "clearly limited to retroviral vectors, while the claims are not so-limited," and (2) that gene of interest is "limited to a 'reporter', and not to any sequence." (Office Action, p. 7). The Office Action concluded that "the Artisan would not have understood Applicant to have been in possession of the claimed invention at the time of filing." (Office Action, p. 7).

Applicants respectfully submit that the Office Action fails to meet its burden to articulate a "reasonable basis challenging the adequacy of the written description" with "findings of fact." The Office Action has not demonstrated how a person skilled in the art would not have understood

Applicants to have been in possession of viral vectors comprising a gene of interest. Consequently, Applicants are under no burden to rebut this rejection. (M.P.E.P. §§ 706.07, 2163, 2163.04). For this reason, Applicants traverse the rejection and respectfully request that the Examiner withdraw the rejection of these claims.

Nevertheless, to expedite the prosecution of these claims to allowance, Applicants now address the Office Action's specific statements.

In response to the Office Action's allegations, Applicants submit that the Specification demonstrates that Applicants had possession of viral vectors comprising a gene of interest. Specifically, Applicants submit that the application is full of such disclosures. For example, paragraph [0102] of the instant Specification specifically states that "the vector can be any vector capable of delivering a nucleic acid to a subject." Paragraph [0092] of the Specification further adds that "other approaches deliver the gene to cells before the cells are delivered to a subject or to tissues prior to implantation." Paragraph [0105] of the Specification additionally explains that "the targeting of tumor endothelium enhances delivery of a reporter and therapeutic genes to tumors." According to paragraph [0116] of the Specification, "the vectors disclosed herein can decrease these effects [meaning complement activation] for gene therapy vectors." In paragraphs [0165]-[0168], the Specification discusses functional nucleic acids, which can include therapeutic genes. Additionally, in paragraph [0226] of the Specification, the Specification provides that "when engineered as vectors, viruses typically have one or more of the early genes removed and a gene or gene/promoter cassette is inserted into the viral genome in place of the removed viral DNA."

Furthermore, the Specification describes (i) retroviral vectors carrying the "DNA of choice," (ii) retroviral "vector[s] containing the gene of interest," (iii) retroviral vectors in which the gag, pol, and env genes "are typically replaced by the foreign DNA that is to be transferred to the target cell," (iv) that the removal of the gag, pol, and env genes "allows for about 8 kb of foreign sequence to be inserted into the viral genome" and that "this amount of nucleic acid is sufficient for the delivery of [] one to many genes," (v) recombinant adenoviral vectors that "achieve high efficiency gene transfer," (vi) adeno-associated viral vectors that contain "at least one cassette containing a promoter which directs cell-specific expression operably linked to a heterologous gene," and (vii) vectors that provide "DNA molecules which are capable of integration into a mammalian chromosome." (*See, e.g.*, paragraphs [0236]-[0239] of the Specification). In view of these disclosures, Applicants submit

that at least these portions of the Specification demonstrate an adequate disclosure. Applicants further submit that at the time of filing, the use of viral vectors to deliver therapeutic genes and other genes of interest was well known in the art.

In view of these teachings as well as the requisite skill in the art, Applicants submit that one of ordinary skill in the art would reasonably conclude that Applicants had possession of viral vectors comprising a "gene of interest." When considered in its entirety and coupled with the state of the art at the time of filing, Applicants' Specification specifically describes the claimed invention in sufficient detail so that one skilled in the art would reasonably conclude that Applicants had possession of the claimed methods and compositions. Thus, the written description requirement is satisfied. Applicants respectfully request that the Examiner withdraw this rejection and allow these claims.

3. Written Description – "targeting motif"

The Office Action rejected Claims 124, 163-164, and 166-175 under 35 U.S.C. 112, first paragraph, as allegedly failing to comply with the written description requirement. Specifically, the Office Action stated that the recitation of "targeting motif" by these claims constituted new matter. (Office Action, p. 8). The Office Action also stated that the support for "targeting motif" as currently claimed was limited to adenoviral vectors. (Office Action, p. 8). Furthermore, the Office Action concluded that "the Artisan would not have understood Applicant to have been in possession of the invention as claimed, for the generic viral vectors encompassed." (Office Action, p. 8).

Applicants respectfully submit that the Office Action fails to meet its burden to articulate a "reasonable basis challenging the adequacy of the written description" with "findings of fact". The Office Action has not demonstrated how a person skilled in the art would not have understood Applicants to have been in possession of viral vectors comprising a targeting motif. For this reason, Applicants traverse the rejection and respectfully request that the Examiner withdraw this rejection and allow these claims.

Nevertheless, to expedite the prosecution of these claims to allowance, Applicants now address the Office Action's specific statements.

Applicants submit that the Specification demonstrates that Applicants had possession of viral vectors comprising a targeting motif. The Specification states that suitable vectors for use in the

claimed invention are vectors that capable of delivering a nucleic acid to a subject. Specifically, the Specification expressly discloses "the viral vector can be a recombinant adenovirus vector, an adeno-associated viral vector, a lentiviral vector, a pseudotyped retroviral vector, a vaccinia vector, an alphavirus vector, or any other viral vector known in the art." (See paragraph 0102 of the Specification). At least in view of this disclosure, Applicants submit that the Office Actions' allegation that only adenoviral vectors are described is incorrect and should be withdrawn.

Furthermore, at the time the application was filed, the art was familiar with at least two concepts. First, that the issue of local delivery is relevant to both efficiency and safety. Second, that the various viral vectors had differing properties. Therefore, while the Specification may exemplify "targeting motifs" for adenoviral vectors (See paragraph 0104 of the Specification), the art was familiar with the (1) tissue-specific delivery of viral vectors, (2) the use of targeting motifs with viral vectors other than adenoviral vectors, and (3) the recombinant DNA techniques used to add a targeting motif to a viral vector.

In view of these teachings, Applicants submit that one of ordinary skill in the art would reasonably conclude that Applicants had possession of viral vectors comprising a "targeting motif" as well as vectors other than adenoviral vectors. When considered in its entirety and coupled with the state of the art at the time of filing, Applicants' Specification describes the claimed invention in sufficient detail so that one skilled in the art would reasonably conclude that Applicants had possession of the claimed methods and compositions. Thus, the written description requirement is satisfied. Applicants respectfully request that the Examiner withdraw this rejection and allow these claims.

4. Written Description – "limitations of claims 173 and 175"

The Office Action rejected Claims 124, 163-164, and 166-175 under 35 U.S.C. 112, first paragraph, as allegedly failing to comply with the written description requirement. Specifically, the Office Action stated that Claims 173 and 175 "encompass generic reporters, and CAR binding site mutations or ablations of integrin binding, to a generic viral vector." (Office Action, p. 9). The Office Action stated that cited paragraphs showed "clearly that the promoter is limitated within the context of the paragraphs describing adenoviral targeting of inflammation." (Office Action, p. 9). The Office Action stated that the support for the CAR binding mutations and ablation of integrin-

binding "is similarly limited to adenovirus." (Office Action, p. 9). The Office Action concluded that the "Artisan would not have understood Applicant to have been in possession of generic invention claimed at the time of the invention." (Office Action, p. 9).

Applicants respectfully submit that the Office Action fails to meet its burden to articulate a "reasonable basis challenging the adequacy of the written description" with "findings of fact". The Office Action has not demonstrated how a person skilled in the art would not have understood Applicants to have been in possession of viral vectors comprising a promoter, CAR binding site mutations, or ablation of integrin-binding. For this reason, Applicants respectfully request that the Examiner withdraw this rejection and allow these claims.

Nevertheless, to expedite the prosecution of these claims to allowance, Applicants now address the Office Action's specific statements.

Applicants submit that the Specification demonstrates that Applicants had possession of viral vectors comprising a promoter. For example, paragraph 0089 of the Specification provides the definition of a promoter and paragraph 0110 of the Specification provides at least one example of a promoter being CMV, a well recognized promoter at the time of filing. In addition, the Specification states that "the method comprises administering to a subject a vector, the vector comprising a reporter nucleic acid operably linked to a promoter nucleic acid . . . ." (paragraph [0018]). The Specification further explains that "the term 'promoter' is defined as a DNA regulatory region capable of binding RNA polymerase in a cell and initiating transcription of a downstream (3' direction) coding sequence." (paragraph 0089 of the Specification). To reiterate, in paragraph [0102], Applicants state that the vector can be any vector capable of delivering a nucleic acid to a subject. Adenoviral vector is one example of such a viral vector. In paragraph 0108 of the Specification, Applicants state that the "promoter can be any promoter which is capable of directing expression in the presence of inflammation." While the Specification enumerates four promoters – Cox1, Cox2, CMV, and flt-1, the Specification does not specifically limit these promoters to adenoviral vectors. Applicants submit that, at the time the application was filed, the art was familiar (1) with the variety of promoters, and (2) with the recombinant DNA techniques used to add or delete various promoters from viral vector constructs.

The Specification also demonstrates that Applicants had possession of viral vectors comprising CAR binding site mutations and ablation of integrin-binding. The art was aware that

CAR was a common cellular receptor for at least two viruses, *e.g.*, coxsackievirus and adenovirus. While the Specification may have provided examples of adenoviral vectors with CAR binding site mutations, by definition, CAR binding site mutations are not limited to adenovirus. Similarly, the ablation of integrin-binding is not limited to adenovirus. Applicants submit that, at the time the application was filed, the art was familiar with both CAR binding site mutations and with the importance of integrin-binding and the effects of the ablation of integrin-biding. Furthermore, the art was familiar with the recombinant DNA techniques used to add or delete CAR binding site mutations from viral vector constructs as well as the recombinant DNA techniques to effect ablation of integrin-binding.

In view of these teachings, Applicants submit that one of ordinary skill in the art would reasonably conclude that Applicants had possession of viral vectors comprising a "promoter," "CAR binding site mutation," or "an ablation of integrin-binding." When considered in its entirety and coupled with the state of the art at the time of filing, Applicants' Specification describes the claimed invention in sufficient detail so that one skilled in the art would reasonably conclude that Applicants had possession of the claimed methods and compositions. Thus, the written description requirement is satisfied. Applicants respectfully request that the Examiner withdraw this rejection and allow these claims.

REJECTION UNDER 35 U.S.C. § 102

The Office Action rejected Claims 124, 170-171, and 173 under 35 U.S.C. § 102(b) as being anticipated by U.S. Patent No. 5,643,770 to Mason *et al.* (herein "Mason"). Applicants respectfully traverse this rejection to the extent that the rejection applies to the claims as amended.

A proper rejection of a claim under 35 U.S.C. § 102(b) requires that a single prior art reference disclose each and every element of the claim. Alternatively, anticipation requires that each and every element of the claimed invention be embodied in a single prior art device or practice. For anticipation, there must be no difference between the claimed invention and the reference disclosure, as viewed by a person of ordinary skill in the field of the invention. (*See, e.g., W.L. Gore & Assoc., Inc. v. Garlock, Inc.*, 220 U.S.P.Q. 303, 313 (Fed. Cir. 1983); *In re Paulsen,* 30 F.3d 1475 (Fed. Cir. 1994); *In re Spada*, 911 F.2d 705 (Fed. Cir. 1990); *Minnesota Min. & Mfg. Co. v. Johnson & Johnson Orthopaedics, Inc.,* 976 F.2d 1559 (Fed. Cir. 1992); *Scripps Clinic & Res. Found. v.*

Genentech, Inc., 927 F.2d 1565 (Fed. Cir. 1991). Thus, in making a rejection under 35 U.S.C. § 102, the Patent Office is burdened with establishing that the cited art teaches each and every limitation of the claims.

Before providing argument against the current rejection, Applicants note that currently pending Claim 124 recites "A method of reducing complement activation during gene therapy in a subject, comprising administering a composition comprising a viral vector comprising a complement modulator displayed on the surface of the vector, wherein the complement modulator inhibits complement activation and wherein the complement modulator is encoded by the viral vector." Applicants respectfully submit that Mason fails to teach such a method or composition.

Mason teaches modified retroviral producer cells that produce retroviral particles for facilitating gene therapy procedures. These procedures involve the transduction of target cells with retroviral vector particles in the presence of complement containing body fluids. (*See, e.g.*, Abstract). Mason also states that "the invention provides modified retroviral vector particles and modified retroviral producer cells producing such particles." (column 13, lines 32-35). Mason elaborates:

> "The modifications involved in making such particles and cells comprise genetic alterations to effect the expression by these cells and particles of complement inhibitor activity. The genetic alterations comprise the introduction of nucleic acid expression constructs directing the expression of retroviral SU (gp70)/complement inhibitor chimeric proteins into cells from which the producer cells are derived.

(column 13, lines 34-42) (emphasis ours). Furthermore, Mason explains that the packaging cells are produced by:

> 1) constructing one or more expression vectors comprising recombinant nucleic acid molecules encoding the retroviral pol, env, and gag proteins (hereinafter referred to as "packaging vectors"); 2) constructing a chimeric vector directing the expression of a chimeric *SU(gp70)/CIM* protein; 3) introducing the one or more packaging vectors and the chimeric vector into cultured cells, typically, mammalian cells; and 4) obtaining the desired packaging cells by selecting those cells of the culture which stably express proteins encoded by the one or more packaging vectors and the chimeric vector.

(column 14, lines 43-54) (emphasis ours). Thus, Mason requires two different vectors (the packaging vector and the chimeric vector) for the transduction of target cells by viral particles that carry a

complement inhibitor sequence. In order for the system of Mason to function, the complement inhibitor sequence must be incorporated into the target cell genome. Once the complement modulator is incorporated into the target cell genome, then the target cell can express the complement modulator, which is responsible for inhibiting or affecting complement. Consequently, the methods disclosed by Mason depend on the transduction of a target cell, and then, the subsequent expression of the complement inhibitor by the target cell. In other words, a complement inhibitor is not encoded by the viral vector.

Thus, Mason is not a teaching of Applicants' currently pending Claim 124. Specifically, Mason fails to teach a method or composition comprising a viral vector comprising a complement modulator displayed on the surface of the vector, wherein the complement modulator inhibits complement activation and wherein the complement modulator is encoded by the viral vector.

For at least these reasons, Applicants respectfully submit that Mason does not teach or disclose each and every element of Applicants' currently pending independent Claim 124. Thus, Mason fails to anticipate Claim 124 and also fails to anticipate currently pending dependent Claims 170-171, and 173. As such, Applicants respectfully request that the Examiner withdraw this rejection and allow these claims.

REJECTION UNDER 35 U.S.C. § 103

I. Combination of Mason, Xing, and Vogels

The Office Action rejected Claims 124, 163, and 170-173 under 35 U.S.C. § 103(a) as being obvious over U.S. Patent No. 5,643,770 to Mason *et al.* (herein "Mason"), Xing *et al.* (2001) Cell Research, 11(2): 116-124, and U.S. Patent No. 7,468,181 to Vogels *et al.* (herein "Vogels"). Applicants respectfully traverse this rejection to the extent that the rejection applies to the claims as amended.

Under 35 U.S.C. § 103(a), the Patent Office bears the burden of establishing a *prima facie* case of obviousness. A *prima facie* case of obviousness requires: (1) that there be a suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine the reference teachings; (2) that there be a reasonable expectation of success; and (3) that the prior art reference (or references when combined) teaches or suggests all of the claim limitations. (*See, e.g.*, M.P.E.P § 2143). The teaching

or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art and cannot be based on Applicants' disclosure. (*See, e.g., In re Vaeck*, 947 F.2d 488 (Fed. Cir. 1991); *In re Fine*, 87 F.2d 1071, 1074 (Fed. Cir. 1988)). Furthermore, rejections based on obviousness grounds cannot be sustained by mere conclusory statements; instead, there must be explicit analysis including some rational underpinning to support the legal conclusion of obviousness. (*K.S.R. Int'l Co. v. Teleflex, Inc.*, 550 U.S. 14 (2007) (citing *In re Kahn*, 441 F.3d 977, 988 (Fed. Cir. 2006)). If the references do not teach each of the claimed elements, then a finding of obviousness fails.

Applicants note that the Office Action applied Mason in the § 103(a) rejection in the same way and for the same disclosure for which the Office Action applied Mason patent in the § 102(b) rejection. For at least the reasons discussed, Mason fails to teach or suggest each and every element of currently amended Claim 124. Specifically, Mason fails to teach or suggest a composition comprising a viral vector comprising a complement modulator displayed on the surface of the vector, wherein the complement modulator inhibits complement activation and wherein the complement modulator is encoded by the viral vector.

The Office Action cited Xing for allegedly teaching that "it is well known that adenoviral vectors suffer from complement-mediated inactivation." (Office Action, p. 13). The Office Action cited Vogels for allegedly teaching that "it is well known to link peptides to be displayed on the surface of an adenovirus." (Office Action, p. 13). Neither Xing nor Vogels cure the deficiencies of Mason. Thus, the combination of Mason, Xing, and Vogels fails to teach or suggest each and every element of currently amended Claim 124, and fails to render as obvious independent Claim 124. As "dependent claims are nonobvious under section 103 if the independent claims from which they depend are nonobvious" (*In re Fine*, 5 U.S.P.Q. 2d 1569, 1600 (Fed. Cir. 1988)), this combination also fails to render as obvious dependent Claims 163 and 170-173. Applicants respectfully request that the Examiner withdraw this rejection and allow these claims.

II. Combination of Mason, Xing, Vogels, and Crystal

The Office Action rejected Claims 124, 163, and 170-173 under 35 U.S.C. § 103(a) as being obvious over U.S. Patent No. 5,643,770 to Mason *et al.* (herein "Mason"), Xing *et al.* (2001) Cell Research, 11(2): 116-124, and U.S. Patent No. 7,468,181 to Vogels *et al.* (herein "Vogels"), and

further in view of U.S. Patent No. 6,127,525 to Crystal *et al.* (herein "Crystal"). Applicants respectfully traverse this rejection to the extent that the rejection applies to the claims as amended.

The Office Action applied Mason, Xing, and Vogels in this § 103(a) rejection in the same way and for the same disclosure for which the Office Action applied these references in the previous § 103(a) rejection. For at least the reasons discussed above, Mason fails to teach or suggest a composition comprising a viral vector comprising a complement modulator displayed on the surface of the vector, wherein the complement modulator inhibits complement activation and wherein the complement modulator is encoded by the viral vector. As explained above, Xing and Vogels fail to cure the deficiencies of Mason. The Office Action cited Crystal for allegedly teaching that "several hypervariable regions of adenovirus may be deleted and/or substituted with chimeric peptides." (Office Action, p. 15). Thus, Crystal does not cure the deficiencies of the combination of Mason, Xing, and Vogels.

Thus, the combination of Mason, Xing, Vogels, and Crystal fails to render as obvious independent Claim 124. As "dependent claims are nonobvious under section 103 if the independent claims from which they depend are nonobvious" (*In re Fine*, 5 U.S.P.Q. 2d 1569, 1600 (Fed. Cir. 1988)), this combination also fails to render as obvious dependent Claims 163 and 170-173. Applicants respectfully request that the Examiner withdraw this rejection and allow these claims.

III. Combination of Mason, Xing, Vogels, and Inal

The Office Action rejected Claims 124, 163, and 169-173 under 35 U.S.C. § 103(a) as being obvious over U.S. Patent No. 5,643,770 to Mason *et al.* (herein "Mason"), Xing *et al.* (2001) Cell Research, 11(2): 116-124, and U.S. Patent No. 7,468,181 to Vogels *et al.* (herein "Vogels"), and further in view of Inal *et al.* (2000) FEBS Letters, 470: 131-134 (herein "Inal"). Applicants respectfully traverse this rejection to the extent that the rejection applies to the claims as amended.

The Office Action applied Mason, Xing, and Vogels in this § 103(a) rejection in the same way and for the same disclosure for which the Office Action applied these references in the previous § 103(a) rejection. For at least the reasons discussed above, Mason fails to teach or suggest a composition comprising a viral vector comprising a complement modulator displayed on the surface of the vector, wherein the complement modulator inhibits complement activation and wherein the complement modulator is encoded by the viral vector. As explained above, Xing and Vogels fail to

cure the deficiencies of Mason. The Office Action cited Inal for allegedly teaching that "the ED1 domain of Sh-Tor inhibits complement and does so when isolated from the normal protein." (Office Action, p. 16). Thus, Inal does not cure the deficiencies of the combination of Mason, Xing, and Vogels.

Thus, the combination of Mason, Xing, Vogels, and Inal Vogels fails to teach or suggest each and every element of currently amended Claim 124, and fails to render as obvious independent Claim 124. As "dependent claims are nonobvious under section 103 if the independent claims from which they depend are nonobvious" (*In re Fine*, 5 U.S.P.Q. 2d 1569, 1600 (Fed. Cir. 1988)), this combination also fails to render as obvious dependent Claims 163 and 169-173. Applicants respectfully request that the Examiner withdraw this rejection and allow these claims.

IV. Combination of Mason, Xing, Vogels, Inal, and Huang

The Office Action rejected Claims 124, 163, 167, and 169-174 under 35 U.S.C. § 103(a) as being obvious over U.S. Patent No. 5,643,770 to Mason *et al.* (herein "Mason"), Xing *et al.* (2001) Cell Research, 11(2): 116-124, U.S. Patent No. 7,468,181 to Vogels *et al.* (herein "Vogels"), Inal *et al.* (2000) FEBS Letters, 470: 131-134 (herein "Inal"), and further in view of Huang *et al.* (2000) Protein Expression and Purification, 18: 169-174 (herein "Huang"). Applicants respectfully traverse this rejection to the extent that the rejection applies to the claims as amended.

The Office Action applied Mason, Xing, Vogels, and Inal in this § 103(a) rejection in the same way and for the same disclosure for which the Office Action applied these references in the previous § 103(a) rejection. For at least the reasons discussed above, Mason fails to teach or suggest a composition comprising a viral vector comprising a complement modulator displayed on the surface of the vector, wherein the complement modulator inhibits complement activation and wherein the complement modulator is encoded by the viral vector. As explained above, Xing, Vogels, and Inal fail to cure the deficiencies of Mason. The Office Action cited Huang for allegedly teaching that "it was well known in the Art that His-Tagged entities can be isolated utilizing the His-Tag." (Office Action, p. 18). Thus, Huang does not cure the deficiencies of the combination of Mason, Xing, Vogels, and Inal.

Thus, the combination of Mason, Xing, Vogels, Inal, and Huang fails to teach or suggest each and every element of currently amended Claim 124, and fails to render as obvious independent

Claim 124. As "dependent claims are nonobvious under section 103 if the independent claims from which they depend are nonobvious" (*In re Fine*, 5 U.S.P.Q. 2d 1569, 1600 (Fed. Cir. 1988)), this combination also fails to render as obvious dependent Claims 163, 167, and 169-174. Applicants respectfully request that the Examiner withdraw this rejection and allow these claims.

V. Combination of Mason, Xing, Vogels, Inal, Huang, and Oh

The Office Action rejected Claims 124, 163, 166-167, and 169-174 under 35 U.S.C. § 103(a) as being obvious over U.S. Patent No. 5,643,770 to Mason *et al.* (herein "Mason"), Xing *et al.* (2001) Cell Research, 11(2): 116-124, U.S. Patent No. 7,468,181 to Vogels *et al.* (herein "Vogels"), Inal *et al.* (2000) FEBS Letters, 470: 131-134 (herein "Inal"), Huang *et al.* (2000) Protein Expression and Purification, 18: 169-174 (herein "Huang"), and in further view of Oh *et al.* (2003) Immunology, 110: 73-79 (herein "Oh"). Applicants respectfully traverse this rejection to the extent that the rejection applies to the claims as amended.

The Office Action applied Mason, Xing, Vogels, Inal, and Huang in this § 103(a) rejection in the same way and for the same disclosure for which the Office Action applied these references in the previous § 103(a) rejection. For at least the reasons discussed above, Mason fails to teach or suggest a composition comprising a viral vector comprising a complement modulator displayed on the surface of the vector, wherein the complement modulator inhibits complement activation and wherein the complement modulator is encoded by the viral vector. As explained above, Xing, Vogels, Inal, and Huang fail to cure the deficiencies of Mason. The Office Action cited Oh for allegedly teaching "that a duplicated ED1 domain provides increased inhibition of complement activation over that of a single ED1 domain." (Office Action, p. 19). Thus, Oh does not cure the deficiencies of the combination of Mason, Xing, Vogels, Inal, and Huang.

Thus, the combination of Mason, Xing, Vogels, Inal, Huang, and Oh fails to teach or suggest each and every element of currently amended Claim 124, and to render as obvious independent Claim 124. As "dependent claims are nonobvious under section 103 if the independent claims from which they depend are nonobvious" (*In re Fine*, 5 U.S.P.Q. 2d 1569, 1600 (Fed. Cir. 1988)), this combination also fails to render obvious dependent Claims 163, 166-167, and 169-174. Applicants respectfully request that the Examiner withdraw this rejection and allow these claims.

VI. Combination of Mason, Xing, Vogels, and Goncalves

The Office Action rejected Claims 124, 163-164, and 170-173 under 35 U.S.C. § 103(a) as being obvious over U.S. Patent No. 5,643,770 to Mason *et al.* (herein "Mason"), Xing *et al.* (2001) Cell Research, 11(2): 116-124, and U.S. Patent No. 7,468,181 to Vogels *et al.* (herein "Vogels"), and in further view of Goncalves *et al.* (2001) Virology, 288(2): 236-246 (herein "Goncalves"). Applicants respectfully traverse this rejection to the extent that the rejection applies to the claims as amended.

The Office Action applied Mason, Xing, and Vogels in this § 103(a) rejection in the same way and for the same disclosure for which the Office Action applied these references in the previous § 103(a) rejection. For at least the reasons discussed above, Mason fails to teach or suggest a composition comprising a viral vector comprising a complement modulator displayed on the surface of the vector, wherein the complement modulator inhibits complement activation and wherein the complement modulator is encoded by the viral vector. As explained above, Xing and Vogels fail to cure the deficiencies of Mason. The Office Action cited Goncalves for allegedly teaching "encapsulation of AAV vectors into Adenoviral envelopes, to thereby allow superior prolonged transgene expression and allowing larger inserts." (Office Action, p. 21). Thus, Goncalves does not cure the deficiencies of the combination of Mason, Xing, and Vogels.

Thus, the combination of Mason, Xing, Vogels, and Goncalves fails to render as obvious independent Claim 124. As "dependent claims are nonobvious under section 103 if the independent claims from which they depend are nonobvious" (*In re Fine*, 5 U.S.P.Q. 2d 1569, 1600 (Fed. Cir. 1988)), this combination also fails to render obvious dependent Claims 163-164 and 170-173. Applicants respectfully request that the Examiner withdraw this rejection and allow these claims.

VII. Combination of Mason, Xing, Vogels, and Legrand

The Office Action rejected Claims 124, 163, 170-173, and 175 under 35 U.S.C. § 103(a) as being obvious over U.S. Patent No. 5,643,770 to Mason *et al.* (herein "Mason"), Xing *et al.* (2001) Cell Research, 11(2): 116-124, and U.S. Patent No. 7,468,181 to Vogels *et al.* (herein "Vogels"), and further in view of U.S. Patent No. 7,256,036 to Legrand *et al.* (herein "Legrand"). Applicants respectfully traverse this rejection to the extent that the rejection applies to the claims as amended.

The Office Action applied Mason, Xing, and Vogels in this § 103(a) rejection in the same way and for the same disclosure for which the Office Action applied these references in the previous § 103(a) rejection. For at least the reasons discussed above, Mason fails to teach or suggest a composition comprising a viral vector comprising a complement modulator displayed on the surface of the vector, wherein the complement modulator inhibits complement activation and wherein the complement modulator is encoded by the viral vector. As explained above, Xing and Vogels fail to cure the deficiencies of Mason. The Office Action cited Legrand for allegedly teaching "adenoviral vectors for use in gene therapy, which are modified in their CAR binding sites." (Office Action, p. 22). Thus, Legrand does not cure the deficiencies of the combination of Mason, Xing, and Vogels.

Thus, the combination of Mason, Xing, Vogels, and Legrand fails to teach or suggest each and every element of currently amended Claim 124, and fails to render as obvious independent Claim 124. As "dependent claims are nonobvious under section 103 if the independent claims from which they depend are nonobvious" (*In re Fine*, 5 U.S.P.Q. 2d 1569, 1600 (Fed. Cir. 1988)), this combination also fails to render as obvious Claims 163, 170-173, and 175. Applicants respectfully request that the Examiner withdraw this rejection and allow these claims.

With this Response, Applicants also submit a Request for Continued Examination, a Petition for an Extension of Time to extend the time period for reply by three-months, and a credit card payment. The credit card payment is in the amount of $960, which represents the $555 small entity fee for a three-month extension of time under 37 C.F.R. § 1.17(a)(3) and the $405 small entity fee for a Request for Continued Examination under 37 C.F.R. § 1.17(e). Applicants submit that this is the correct amount due; however, Applicants authorize the Commission to charge to Deposit Account No.14-0629 any additional fee that may be required, or to credit to the same account any overpayment of fees.

Respectfully submitted,

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